Remarks

Claims 56-80 and 85-114 are pending in the subject application. Applicants acknowledge that claims 59, 60, 86-110, 112 and 114 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have amended claims 57, 59, 66, 100 and 104 and added new claims 115-118. Support for the amendments can be found throughout the subject specification and in the claims as originally filed (see, for example, pages 30-35, Examples D-F and Example I). Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 56-80 and 85-118 are currently before the Examiner (with claims 59, 60, 86-110, 112 and 114 standing withdrawn from consideration). Favorable consideration of the pending claims is respectfully requested.

Applicants gratefully acknowledge the Examiner's withdrawal of the rejection under 35 U.S.C. § 112, first paragraph. Applicants also request the courtesy of an interview in this matter prior to the issuance of another Office Action.

Claims 56-58, 61-63, 66-71, 73-77, 80, 85, 111 and 113 remain rejected under 35 U.S.C. § 102(b) as anticipated by Namen *et al.* (U.S. Patent No. 5,328,988). In addition, claims 56-58, 61-63, 66-71, 73-75, 78-80, 85, 111 and 113 are rejected under 35 USC §102(b) as anticipated by Ho *et al.* (U.S. Patent No. 5,714,141). The Office Action reiterates that Namen *et al.* teach a pharmaceutical composition comprising a substantially homogeneous recombinant human IL-7 polypeptide free of contaminating endogenous materials and Ho *et al.* teach a pharmaceutical composition comprising a highly purified recombinant human IL-7 in combination with a vaccine, *e.g.*, Hepatitis B vaccine. The Office Action states that while Namen *et al.* is silent about the disulfide bond positions, this structural feature would reasonably have been considered to be inherent to the human IL-7 molecule since the tertiary structure of a protein is an intrinsic feature resulting from its primary structure. Applicants respectfully assert that neither the Namen *et al.* nor the Ho *et al.* patents anticipate the claimed invention for the reasons that follow.

The Office Action states that while Namen *et al.* is silent about the disulfide bond positions, this structural feature would reasonably have been considered to be inherent to the human IL-7 molecule since the tertiary structure of a protein is an intrinsic feature resulting from its primary structure. "In relying on the theory of inherency, the examiner must provide a basis-in-fact and/or

technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art." *Ex parte Levy*, 17 USPQ2d 1461, 1464 (Bd. Pat. App. & Inter. 1990) (emphasis in original). Under the doctrine of inherency, if an element is not expressly disclosed in a prior art reference, the reference will still be deemed to anticipate a subsequent claim if the missing element '**is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill**.'" *Rosco, Inc. v. Mirror Lite Co.*, 304 F.3d 1373, 1380 (Fed. Cir. 2002)(emphasis added)(*quoting Cont'l Can Co. v. Monsanto Co.*, 948 F.2d 1264, 1268 (Fed. Cir. 1991)). "Inherent anticipation requires that the missing descriptive material is 'necessarily present,' not merely probably or possibly present, in the prior art." *Trintec Indus., Inc. v. Top-U.S.A. Corp.*, 295 F.3d 1292, 1295 (Fed. Cir. 2002) (quoting *In re Robertson*, 169 F.3d 743, 745 (Fed. Cir. 1999)).

The claims recite a composition of matter comprising a human or simian IL-7 conformer, wherein said conformer **comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141), wherein the total amount by weight of said IL-7 conformer in said composition of matter is at least 98% by weight** and wherein said composition of matter is substantially free of IL-7 molecular variants or product related impurities (emphasis added). In this case, the Patent Office has not provided any basis-in-fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic of the prior art IL-7 compositions necessarily flows from the teachings of the applied prior art and that the IL-7 compositions of Namen *et al.* and/or Ho *et al.* contain at least 98%, by weight, of an IL-7 conformer that comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141). As also noted in the as-filed specification (at page 9):

> ... in 1997, from MALDI Mass spectrometry analysis of a human IL-7 produced by recombinant technology and from site directed mutagenesis exchanging serine for cysteine, Cosenza and colleagues established the assignment of the three disulfide bridges to the positions 1-6; 2-5; 3-4, in a way fully analogous to the intra-molecular disulfide bridges experimentally determined for IL-4 (Cosenza L. et al.; Protein Science; 2000; 9:916-926 – Walter M.R. et al.; Journal of Biological Chemistry; 1992; 267:20371-20376). In this work, the mass spectrometry analysis of the peptide digest of the recombinant native molecule clearly demonstrated the reality of the Cys2-Cys141 (1-6) disulfide bridge and the site directed mutagenesis established the critical role for bioactivity of the Cys2-Cys141 (1-6) and Cys47-Cys92 (3-4) bridges.

> The two Cys/Ser IL-7 mutants allowing these two single bridges were able to show a good bioactivity (EC50 of $4x10^{-9}$ and $2x10^{-9}$ M) in the bioassay in comparison to EC50 of $2x10^{-10}$ for the three disulfide bridges molecule 1-6; 2-5; 3-4. Based on these experimental results, these three disulfide bridges 1-6; 2-5; 3-4 were assigned to the human Interleukin-7 and filed into the international protein data bank (Swiss Prot P13232, PDB code 1IL7).

Thus, it is respectfully submitted that the assertion in the Office Action is speculative, at best, that the compositions of Namen *et al.* and Ho *et al.* anticipate the claimed composition of matter "comprising a human or simian IL-7 conformer, wherein said conformer comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141), wherein the total amount by weight of said IL-7 conformer in said composition of matter is at least 98% by weight and wherein said composition of matter is substantially free of IL-7 molecular variants or product related impurities and wherein the human IL-7 conformer is not immunogenic in humans and the simian IL-7 conformer is not immunogenic in non-human primates", especially in view of the state of the art which recognizes the following disulfide bonding pattern: Cys: 1-6 (Cys2-Cys141); 2-5 (Cys34-Cys129); 3-4 (Cys47-Cys92) (see print-out for UniProtKB/Swiss-Prot Entry P13231, supplied in the previous response, and the as-filed specification at page 9, lines 19-22), and the Office Action provides no evidence that persons of ordinary skill in the art would recognize that the compositions of Namen *et al.* and Ho *et al.* contain any of the claimed conformers.

In column 13, from line 9 to line 22, Namen *et al.* describes his purification process when IL-7 is produced from a recombined *E. coli* strain. This process is easily comparable to the process described by Cosenza *et al.* (1997) who also use a recombined *E. coli* strain as described on the following pages of their publication: a) p. 32996: *Expression and Purification of hIL-7 to Maldi Mass Spectrosopy...* and b) p. 32997: left column *Refolding hIL-7* into a Biologically Active Conformation. The table below shows the similarities of the two processes:

NAMEN *et al.*	**COSENZA *et al.***	**COMPARABILITY**
Recombined *E. coli* strain	Recombined *E. coli* strain	Identical
Cell collection with pellet disruption sonication or freezing	Cell disruption by pellet freezing followed by sonication	Identical
Extraction of cell pellets Preliminary concentration Salting out	Extraction of inclusion bodies and denaturation by 5 M guanidinium chloride	Similar; more details described by Cosenza
Aqueous ion exchange or Size exclusion chromatography	Purification by Size Exclusion HPLC	Identical
Renaturation at 10 to 50µg/ml with 1 to 6M guanidine Chloride	Refolding with glycine L arginine DTT and dialysis	Equivalent; more details described by Cosenza
HPLC final purification	HPLC final purification: HPLC sizing followed by C4 RP HPLC	Similar

After completing his production and purification process, closely similar to Namen *et al.* description, Cosenza *et al.* analyzed the resulting purified recombinant human IL-7 for disulfide bonds formation by tryptic digestion of the protein in non denaturing conditions followed by peptide mass determination using MALDI TOF mass spectrometry (see page 32999, bottom left, *Discussion*). In Table II of his paper, Cosenza *et al.* was able to detect peptides 1 and 23 which are linked by a disulfide bond, thereby establishing the proof of the 1-6 (Cys3-Cys142) bridge (equivalent to Cys 2-Cys141 for non methionyl amino terminal IL-7). These two peptides could not be found after digestion in presence of the reducing agent DTT. Applicants submit that this provides evidence that one skilled in the art **would not have recognized** that the compositions of Namen *et al.* or Ho *et al.* contained 98%, by weight, of a human or simian IL-7 conformer, having the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141); rather, this would have suggested to one skilled in the art that the compositions of Namen *et al.* and Ho *et al.* would have had the following disulfide bonding pattern: Cys: 1-6 (Cys2-Cys141); 2-5 (Cys34-Cys129); 3-4 (Cys47-Cys92). Accordingly, reconsideration and withdrawal of the rejection of record is respectfully requested.

Applicants further note that Namen *et al.* teach that various bands are detected by SDS gel analysis at the end of his purification process. Specifically, Namen *et al.* state (column 19, line 13) "a number of proteins were still present", among which a minor "faint" band above the major band was associated with bioactivity. Applicants submit that this clearly demonstrates that the compositions of Namen *et al.*, although bioactive, are not a highly purified specific IL-7 conformer compatible with lack of immunogenicity. Accordingly, reconsideration and withdrawal of the rejections under 35 U.S.C. § 102(b) is respectfully requested.

Additionally, Namen *et al.* describe various generic techniques to prepare recombinant IL-7, either from recombinant microorganisms or from recombinant mammalian cells. Applicants note that Ho *et al.* state that IL-7 can be produced according to methods known in the art (column 8, paragraph 1). Ho *et al.* also state that IL-7 used in the examples was purchased from Immunex (Example 2, paragraph 1) and Applicants note that the Namen *et al.* patent cited as the basis of the rejection was owned by Immunex (see assignee information) . Thus, because Ho *et al.* used IL-7 produced by Immunex, Applicants have provided a comparison of IL-7 compositions prepared according to the teachings of Namen *et al.* (reproduced to the greatest extent possible) and a method known in the art at the time the Ho *et al.* application was filed on the basis of the U.S. Patent No. 4,965,195 (to Namen *et al.* and identified in the priority chain of the cited Namen patent) in an effort to compare the compositions of Ho *et al.* and Namen *et al.* (presumed to be the same on the basis of the teachings in Ho et al. indicating that their IL-7 composition was purchased from Immunex) to the claimed compositions. In the attached Declaration, Brigitte Assouline, an inventor of the presently claimed invention, explains and shows that none of these processes of making IL-7, be it in prokaryotic or in eukaryotic cells, leads to the production of a composition of matter comprising a human or simian IL-7 conformer, wherein said conformer **comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141), wherein the total amount by weight of said IL-7 conformer in said composition of matter is at least 98% by weight**. Thus, it is respectfully submitted that the IL-7 compositions of Namen et al. and Ho et al. do not anticipate the claimed composition.

Claims 64 and 65 remain rejected under 35 U.S.C. § 103(a) as obvious over Namen *et al.* (U.S. Patent No. 5,328,988) or Ho *et al.* (U.S. Patent No. 5,714,141) in view of Goeddel *et al.* (U.S.

Patent No. 5,223,408). The Office Action states that Goeddel *et al.* cure the deficiency of the prior art by teaching conjugating an IL-7 polypeptide with IgG1-Fc or albumin to increase half-life and it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use an IgG1-Fc or albumin conjugated IL-7 polypeptide, which has an increased half-life, in the prior art compositions. Claim 72 remains rejected under 35 U.S.C. § 103(a) as obvious over Ho *et al.* (U.S. Patent No. 5,714,141) in view of Morozov *et al.* (U.S. Patent No. 5,728,680). The Office Action asserts that Morozov *et al.* cure the deficiency of the prior art by teaching formulating pharmaceutical compositions containing Hepatitis B vaccine with excipients, such as sodium citrate so it would have been *prima facie* obvious to one of ordinary skill in the art to include excipients, such as sodium citrate, in the prior art composition that contains rh-IL-7 and Hepatitis B vaccine. Applicants respectfully assert that the claimed invention is not obvious over the cited references. As noted above, neither Namen *et al.* nor Ho *et al.* teach a composition of matter comprising a human or simian IL-7 conformer, wherein said conformer **comprises the following three disulfide bridges: Cys: 1-4 (Cys2-Cys92); 2-5 (Cys34- Cys129) and 3-6 (Cys47-Cys141), wherein the total amount by weight of said IL-7 conformer in said composition of matter is at least 98% by weight** and wherein said composition of matter is substantially free of IL-7 molecular variants or product related impurities (emphasis added). Applicants further submit that neither Goeddel *et al.* nor Morozov *et al.* cure this deficiency in the teachings of Namen *et al.* and Ho *et al.* Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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FCE/jb/sl

Attachment: Declaration Pursuant to 37 C.F.R. §1.132 of Brigitte Assouline